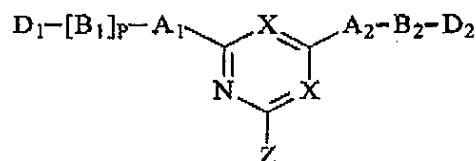


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Docket No. GJE-82
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1 (original). An affinity ligand-matrix conjugate comprising the matrix and, conjugated thereto by the group Z, a ligand having the general formula (I):



wherein one X is N and the other X is N, CCl or CCN;

A₁ and A₂ are each independently O, S or N-R₁ and R₁ is H, C₁₋₆ alkyl, C₁₋₆ hydroxyalkyl, benzyl or β-phenylethyl;

B₁ and B₂ are each independently an optionally substituted hydrocarbon linkage containing from 1 to 10 carbon atoms;

D₁ is H or a primary amino, secondary amino, tertiary amino, quaternary ammonium, imidazole, guanidine or amidino group; and

D₂ is a secondary amino, tertiary amino, quaternary ammonium, imidazole, guanidine or amidino group; or

B₂-D₂ is -CHCOOH-(CH₂)₃₋₄-NH₂; and

p is 0 or 1;

with the proviso that, when each X is N, A₁ is NR₁, A₂ is NH, B₂ is phenyl, D₁ is H, D₂ is amidino and p is zero, then R₁ is not methyl, β-phenylethyl or β-hydroxyethyl.

2 (previously amended). The conjugate according to claim 1, wherein A₁ and A₂ are each independently N-R₁ wherein R₁ is H, C₁₋₆ alkyl, C₁₋₆ hydroxyalkyl, benzyl or β-phenylethyl.

3 (previously amended). The conjugate according to claim 2, wherein A₁ and A₂ are each NH.

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4 (previously amended). The conjugate according to claim 1, wherein B₁ and B₂ are each independently -CHCOOH-(CH₂)₁₋₄ or a divalent ethyl, propyl, 2-hydroxypropyl, butyl, pentyl, hexyl, phenyl, naphthyl or cyclohexyl group.

5 (previously amended). The conjugate according to claim 4, wherein B₁ and B₂ are each independently -CHCOOH-(CH₂)₃₋₄ or a divalent butyl, pentyl or phenyl group.

6 (previously amended). The conjugate according to claim 4, wherein B₁ and B₂ are each independently -CHCOOH-(CH₂)₃₋₄ and p is 1.

7 (previously amended). The conjugate according to claim 1, wherein D₁ is H, amino, imidazolyl, guanidine, aminidino, trimethylammonium, triethylammonium, dimethylamino, diethylamino, methylamino or ethylamino.

8 (previously amended). The conjugate according to [any preceding] claim 1, wherein D₂ is imidazolyl, guanidine, aminidino, trimethylammonium, triethylammonium, dimethylamino, diethylamino, methylamino or ethylamino.

9 (previously amended). The conjugate according to claim 1, wherein p is 1.

10 (previously amended). The conjugate according to claim 1, wherein each X is N.

11 (previously amended). The conjugate according to claim 1, wherein Z is



wherein T is O, S or NR₂ and R₂ is H or C₁₋₆ alkyl;

V is O, S, -COO-, CONH, NHCO, -PO₃H-, NH-arylene-SO₂-CH₂-CH₂- or N-R₃ and R₃ is H or C₁₋₆ alkyl;

L is an optionally substituted hydrocarbon linkage containing from 2 to 20 carbon atoms; and
m is 0 or 1.

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12 (previously amended). The conjugate according to claim 11, wherein R_2 and R_3 are each H.

13 (previously amended). The conjugate according to claim 11, wherein T is O or NH.

14 (previously amended). The conjugate according to claim 13, wherein T is NH.

15 (previously amended). The conjugate according to claim 1, wherein m is 1 and L is a divalent butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl or dodecyl group.

16 (previously amended). The conjugate according to claim 11, wherein m is 1 and V is O, -CONH-, -NHCO- or N- R_3 .

17 (previously amended). The conjugate according to claim 16, wherein V is O or NH.

18 (previously amended). The conjugate according to claim 17, wherein V is NH.

19 (previously amended). The conjugate according to claim 17, wherein Z-M (M being the matrix) is $-NH-(CH_2)_{4-10}-NH-M$.

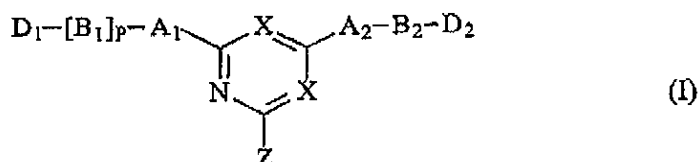
20 (previously amended). The conjugate according to claim 19, selected from any of formulae XXX to XXXX.

21 (previously amended). The conjugate according to claim 1, wherein the matrix is optionally tresyl-activated, sulphonyl chloride-activated, tosyl-activated, vinyl sulphone-activated or epoxy-activated.

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22 (previously amended). An affinity ligand of general formula (I):



wherein one X is N and the other X is N, CCl or CCN;

A₁ and A₂ are each independently O, S or N-R₁ and R₁ is H, C₁₋₆ alkyl, C₁₋₆ hydroxyalkyl, benzyl or β-phenylethyl;

B₁ and B₂ are each independently an optionally substituted hydrocarbon linkage containing from 1 to 10 carbon atoms;

D₁ is H or a primary amino, secondary amino, tertiary amino, quaternary ammonium, imidazole, guanidine or amidino group; and

D₂ is a secondary amino, tertiary amino, quaternary ammonium, imidazole, guanidine or amidino group; or

B₂-D₂ is -CHCOOH-(CH₂)₃₋₄-NH₂; and

p is 0 or 1; and

wherein Z is a functional group capable of reaction with a solid matrix; and with the proviso that, when each X is N, A₁ is NR₁, A₂ is NH, B₂ is phenyl, D₁ is H, D₂ is amidino and p is zero, then R₁ is not methyl, β-phenylethyl or β-hydroxyethyl.

23 (previously amended). The ligand according to claim 22, wherein the matrix is optionally tressyl-activated, sulphonyl chloride-activated, tosyl-activated, vinyl sulphone-activated or epoxy-activated.

24 (previously amended). The ligand according to claim 22, wherein Z is F, Cl, Br or I.

25 (previously amended). The ligand according to claim 22, wherein Z is -NH-(CH₂)₂₋₂₀-NH₂.

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26 (previously amended). The ligand according to claim 22, wherein Z is $-\text{NH}-(\text{CH}_2)_{2-20}-$
 $(\text{CO})_{0-1}-\text{OH}$.

27 (previously amended). The ligand according to claim 22, wherein Z is
 $-\text{T}[\text{L}-\text{V}]_m-\text{R}_{10}-\text{CR}_{11}=\text{CH}_2$

wherein T is O, S or NR_2 and R_2 is H or C_{1-6} alkyl;

V is O, S, $-\text{COO}-$, CONH , NHCO , $-\text{PO}_3\text{H}-$, $\text{NH-arylene-SO}_2-\text{CH}_2-\text{CH}_2-$ or N-R_3 and R_3 is H
or C_{1-6} alkyl;

L is an optionally substituted hydrocarbon linkage containing from 2 to 20 carbon atoms;

m is 0 or 1;

R_{10} is CO , CH_2 , NH-CH_2- or $-\text{S-CH}_2-$; and

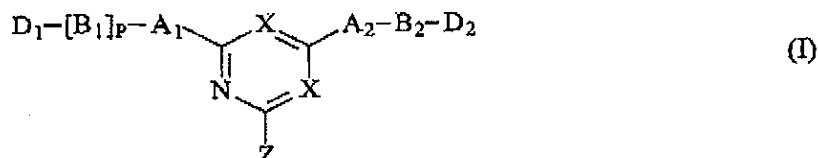
R_{11} is H or C_{1-6} alkyl.

28 (previously amended). The ligand according to claim 24, wherein Z is Cl, and each X is
N.

29 (previously amended). The ligand according to claim 28, wherein each X is N.

30 (previously amended). The ligand according to claim 22, selected from any of formulae
XVI to XXVI.

31 (currently amended). A method for the removal, separation, isolation, purification,
characterization, identification or quantification of an endotoxin; wherein said method utilizes an
affinity ligand or conjugate having the general formula (I):



wherein one X is N and the other X is N, CCl or CCN;

Z is a functional group capable of reaction with a solid matrix;

A₁ and A₂ are each independently O, S or N-R₁ and R₁ is H, C₁₋₆ alkyl, C₁₋₆ hydroxyalkyl, benzyl or β-phenylethyl;

B₁ and B₂ are each independently an optionally substituted hydrocarbon linkage containing from 1 to 10 carbon atoms;

D₁ is H or a primary amino, secondary amino, tertiary amino, quaternary ammonium, imidazole, guanidine or amidino group; and

D₂ is a secondary amino, tertiary amino, quaternary ammonium, imidazole, guanidine or amidino group; or

B₂-D₂ is -CHCOOH-(CH₂)₃₋₄-NH₂; and

p is 0 or 1.

32 (previously amended). The method according to claim 31, for the removal of an endotoxin from water or an aqueous solution, body fluid, blood, plasma, solution of pharmaceutical products, protein or other compound of biological origin.

33 (previously amended). The method according to claim 32, which comprises using the conjugate for the extracorporeal removal of endotoxin from whole blood or plasma, prior to re-infusion into the donor or another recipient.

34 (previously amended). The method according to claim 31, wherein the endotoxin originates from a Gram-negative bacterium.

35 (previously amended). The method according to claim 31, in an endotoxin-containing solution or liquid is applied to the conjugate at a pH of 1.0 to 13.0.